# ASBMT Raises Concerns About FDA Draft Rules for "Good Tissue Practices"

The American Society for Blood and Marrow Transplantation (ASBMT) has submitted comments to the U.S. Food and Drug Administration, raising concerns about specific requirements in proposed new rules for "good tissue practices."

The draft regulations address methods, facilities and controls in the manufacture of human cellular and tissue-based products. They include labeling requirements, reporting of product deviations and adverse reactions, and FDA inspections to enforce compliance. Certain cellular and tissue-based products that require licensing or pre-market approval as biological products or medical devises would be subject to new additional requirements.

The draft rules are the concluding phase of a 1997 FDA initiative addressing safety and product quality in human cellular and tissue-based products.

Joining ASBMT and other organizations submitting comments to the agency was the Foundation for Accreditation of Hematopoietic Cell Therapy (FAHCT), which is co-sponsored by ASBMT.

Although most of the elements in the draft regulations conform to voluntary standards already adopted by FAHCT, certain components are discrepancies and differences that could have a negative impact on blood and marrow transplantation, according to the ASBMT statement.

"Because ASBMT uniquely represents the physicians who administer transplants and care for these patients prior to, during and after transplantation, we feel it important to summarize those components of the rules proposed by the FDA that exceed the requirements of FAHCT Standards that will have an untoward impact on the practice of transplantation medicine and potentially inhibit effective application and continued development of allogeneic hematopoietic stem cell transplants," said ASBMT President Richard O'Reilly, M.D.

Among the ASBMT recommendations to the FDA were:

- Guarantees that patient-specific information remains confidential and does not become part of a public record or file.
- Elimination of certain oversight and audit requirements that would be onerous for smaller transplant centers.
- Elimination of required advance justification and authorization for procedure deviations.
- Elimination of separate reporting of cleaning and disinfection for each reagent and with each piece of validated equipment.
- Simpler labeling requirements for individual transplant products.
- Revision of proposed requirements for expiration dates on cryopreserved transplants.
- Modification of required reports of adverse reactions, to make them more practical and specific to blood and marrow transplantation.
- Elimination of a requirement that peripheral and marrow-derived blood stem cells imported to the United States must be held for inspection by an FDA official at the port of entry.

The ASBMT statement also questioned the accuracy of the FDA's characterization of the risks of contamination in hematopoietic progenitor cell products and the agency's estimates of costs to comply with the proposed regulations. "The FDA presents no convincing evidence that requirements exceeding the FAHCT Standards will significantly alter the incidence of contaminated peripheral blood progenitor cell and marrow cell samples, an incidence no higher than that recorded for current transfusion practice," Dr. O'Reilly said.

Both ASBMT and FAHCT are concerned that the agency's estimates for rates of infection are inflated, and that the projected costs for compliance are underestimated. A FAHCT-conducted analysis of compliance costs indicates about $27,000 in new expenditures for compliant centers and nearly $80,000 for non-compliant centers. The total added costs for the BMT field would exceed $16 million.

The ASBMT statement concluded that the proposed new rules offer little benefit over current FAHCT Standards, but would substantially add to costs, a burden not likely to be shouldered by third-party insurers.

Following are the complete texts of the ASBMT and FAHCT statements submitted to the FDA.

# ASBMT Letter to the Food and Drug Administration

May 7, 2001

Food & Drug Administration Docket
Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD 20852

**Re: 21 CFR Part 1271 [Docket No. 97N-484P]: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement**

Dear Sirs/Madams:

I am writing as President of the American Society of Blood and Marrow Transplantation, an organization dedicated to the continued development of blood and marrow transplantation approaches, their increased safety and efficacy when applied to lethal disorders of the hematopoietic system, and other sensitive tumors. This organization represents nearly 1,000 members in the transplant community derived from over 250 transplant centers in the United States and in North and South America.

Our group has extensively reviewed the proposed regulations for 21CFR part 1271 in entitled, "Current Good Tissue Practice For Manufacturers of Human Cellular and Tissue Based Products; Inspection and Enforcement; Proposed Rule." For most of the proposed rules, we congratulate the FDA for its balanced approach and its development of appropriate and practicable standards for the production of hematopoietic stem cells for transplantation purposes.

We are also impressed that the vast majority of the rules proposed have already been incorporated in the standards and guidelines proposed by the American Society for Bone Marrow Transplantation and the International Society of Hematopoietic Graft Engineering (ISHAGE) through its accrediting body, the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT).

As you know, FAHCT was established in 1994 to specifically provide standards and guidelines for the transplantation community. To insure appropriate evaluation and accreditation, FAHCT has established training programs and has also selected and developed a panel of 300 laboratory and clinical experts in hematopoietic stem cell preparation and transplantation to conduct the inspections of each center applying for accreditation. The guidelines developed and adopted by FAHCT form the basis for each center's accreditation. These guidelines are now widely accepted throughout this country and Europe and indeed have been approved by most of the major cooperative treatment groups participating in multicenter trials of transplantation in the treatment of malignancies under the auspices of the NIH and the National Cancer Institute.

In reviewing the proposed rules, we also note, however, several important discrepancies and differences between the standards and guidelines formulated and adopted by FAHCT and those proposed in the new rules by the FDA. The joint response of FAHCT, ASBMT and ISHAGE has already detailed the several points in the proposed FDA rules which either deviate from or are not required by the FAHCT Standards, which raise concerns in the laboratories providing hematopoietic stem cell grafts. Because ASBMT uniquely represents the physicians who administer transplants and care for these patients prior to, during, and after transplantation, we feel it important to summarize those components of the rules proposed by the FDA that exceed the requirements in the FAHCT Standards that will have an untoward impact on the practice of transplantation medicine and potentially inhibit effective application and continued development of allogeneic hematopoietic stem cell transplants in the treatment of patients.

These points of concern, in the order of their presentation in the proposed rules, are:

**1) Sections 1271.160 (b) Functions (7) paragraph 2 and Sections 1271.320 (b) Complaint File. File review and copying by the FDA.**

The requirement for reports of periodic reviews and analyses of product directions and for maintenance of a complaint file for review upon request by the FDA reflects the need for quality management tools by facilities producing hematopoietic stem cells for transplantation. We accept this need. However, it is essential that these functions permit open and frank reviews. Such reviews within individual centers are privileged, confidential, and not a part of the public record. The FDA should specify in the final rule that the FDA and its employees will guarantee the confidentiality of these reports and that these reports will not become part of the public file regarding a center producing or distributing the cell product.

**2) Section 1271.160 (c and d) Authority Over Program and Audits**

The requirement for oversight and audits by individuals not engaged in the work of the hematopoietic stem cell processing laboratory will be difficult and may not be practicable for small facilities, where only 1-2 individuals may do this type of work. If independent oversight and audits are required, individuals at a center not expert in the issues would likely be recruited. Alternatively, outside experts would need to be recruited at a cost that would likely be prohibitive. These requirements are onerous and might well significantly reduce the number of donor centers currently participating in the National Marrow Donor Program, which currently provides up to 30% of the transplants administered worldwide. For these reasons, we would recommend that this requirement be dropped.

**3) Section 1271.180 Procedures.**

"Any deviation from a procedure shall be authorized in advance by a responsible person, recorded and justified." Because of donor to donor variation in yields of hematopoietic stem cells and occasionally, the responses of blood cells to standardized fractionation procedures, it is not possible to predict and authorize deviations in advance. In the context of a hematopoietic stem cell transplant, this is particularly the case, since the transplant from a given identified donor must be administered within 1-2 days of completion of myeloablative cytoreduction. Given these circumstances, we would respectfully recommend that this rule be deleted.

**4) 1271.195 Environmental Control and Monitoring (a) General and (e) Records.**

The intent of these rules is appropriate, and most of the specific requirements are already part of the FAHCT guidelines. However, certain features of the rules need to be revised to make them practicable and not inappropriately burdensome.

Given the fact that the papers cited by the FDA regarding the incidences of contamination of both manipulated and unmanipulated hematopoietic stem cell preparations derived from marrow and blood quote rates which are not different from those published for conventional blood products such as platelets and red cells, vide infra it is unduly onerous to require the cleaning and disinfection of rooms and equipment that is required for drug manufacture for facilities processing multiple individual hematopoietic stem cell products when other control systems such as HEPA filtered laboratory hood, are in place to prevent contamination. Procedures and systems such as are called for by FAHCT and AABB for blood cell processing facilities are and should be sufficient.

Similarly, the demand for record keeping which may be useful in the manufacture of large lots of drugs is unduly burdensome and non-practicable for a facility producing small or large numbers of individual hematopoietic stem cell components. The processing records for each stem cell preparation should, as requested by FDA and FAHCT Standards, identify supplies and reagents used for processing. The converse, that is, to have separate records of each transplant prepared with each reagent and with each piece of validated equipment, is prohibitively time-consuming. Again, we believe this requirement should be dropped and that the guidelines recommended by FAHCT would be sufficient.

**5) 1271.220 Process Controls (b) Processing Material and (c) Pooling.**

(b) The section on Processing Material should be amended to state that validated procedures shall be established to insure the appropriate use and removal of processing material and that the use of these procedures in the preparation of the stem cells be documented. It is not possible for a center to test, on a case by case basis, that processing materials have actually been eliminated.

(c) The section on pooling is appropriate for hematopoietic stem cell fractionation as it is currently practiced. However, with the current development of several strategies for inducing transplant anergy and, conversely, for generating donor type alloreactive T-cells and T-cells specific for a patient's cancer for adoptive cell therapy, this rule will soon be outdated and restrictive. Rewording of the rule to include the phrase "Unless required by a specialized approved protocol…." Would avoid these future restrictions and facilitate rather than inhibit progress.

**6) 1271.250 Labeling Controls**

These rules need to be streamlined along lines required by FAHCT and AABB which provides for coded identification of donor, identification of intended recipient and critical information regarding donor suitability and the type of processing used. The information called for in the rule is exorbitant for identification of individual transplant products.

**7) 1271.260 Storage**

Expiration dates are appropriate for conventional blood products, or drugs with defined shelf-lives. At present, the shelf-life of appropriately cryopreserved hematopoietic stem cells from peripheral blood, marrow or umbilical cord blood is not established. The rule needs to be revised to reflect this. Arbitrary assignment of expiration dates for such cryopreserved transplants is, at this stage, unjustified.

**8) 1271.350 (a) Adverse Reaction Reports**

The requirement for reporting any adverse reaction that necessitates medical or surgical intervention goes well beyond current FDA guidelines for reporting adverse drug reactions. Furthermore, since transplants of marrow, peripheral blood stem cells and umbilical cord cells can be rejected and conversely, often cause reactions such as graft vs. host disease, which can be fatal, this rule needs to be revised and better targeted.

**9) 1271.420 Human cellular and tissue-based products offered for import (b)**

This rule specifies that imported hematopoietic stem cell transplants would each have to be held until released by the FDA.

The rule is not acceptable to the hematopoietic stem cells transplant community. Unless there is an FDA officer available every minute of every day and night to immediately approve the 2000-3000 unrelated marrow and PBSC transplants that enter or leave this country each year, it cannot and must not be enacted. Marrow and peripheral blood stem cells are highly perishable. More importantly, the potential recipient of such a transplant will have completed supralethal myeloablative conditioning by the time the transplant arrives. To have such a transplant on hold, while an official at an airport tries to contact an FDA official to approve its import is, at this stage in the history of unrelated hematopoietic stem cell transplants, unethical and serves no useful purpose.

In addition to the enclosed specific comments, requests and suggestions regarding the proposed rules, we also wish to express, for the record, the serious concerns and reservations of the transplant community regarding the accuracy of the FDA's estimates of the risks associated with hematopoietic stem cell transplants in the absence of the proposed rules and the costs and benefits of implementing these rules as proposed.

While we completely concur with the FDA's objective of providing safe transplants with the lowest possible risk of microbial contamination, a perusal of available literature and a critical review of the papers cited on page 1547 of the proposed rules indicates that the risks to transplant recipients are greatly overestimated.

First, it should be noted that the peripheral blood progenitor cells and marrow cell samples described in the papers by Webb et al and by Espinosa et al were largely derived from autologous donors who had received multiple prior therapies, and, indeed, often required multiple harvests to obtain targeted doses of stem cells (82% in the series quoted by Webb et al., 97% in that of Espinosa et al). This is an important aspect of these studies, since many of these patients likely had low counts at time of harvest, would be likely to have had an indwelling catheter for extended periods prior to harvest, and would be at high risk for catheter infection at time of harvest. Thus, the risks of contamination quoted for PBMC (2.4% for Webb et al.; 0.2% for Espinosa et al.) would be expected to be at the highest end of frequencies. In fact, the incidences quoted are, in one case, no higher than, and in the other, lower than the incidences of contaminated blood products reported in several series for platelet or red blood cell transfusions. Strikingly also, the rate of contamination for monoclonal antibody treated and CD34 selected cells reported by Webb et al did not differ significantly from that of unmanipulated peripheral blood stem cells collected like a normal leukapheresis in a totally closed system.

Based on the data presented, there is no convincing evidence to suggest that the added rules called for will significantly alter the incidence of contaminated peripheral blood progenitor cell and marrow cell samples, since it is no higher than that recorded for current transfusion practice.

As an aside, it should also be noted that the autologous stem cell factions described by Webb et al and Espinosa et al would not be subject to the proposed FDA rules.

Secondly, the rates of infection quoted in the FDA document are inflated. While 13.7% of patients developed fever in the early post transplant period, only 2.73% were actually culture positive. In the two cases reported, the organism in the stem cell graft was subsequently cultured from the patient. As in all other reported series, the infection was effectively treated by antibiotics. In no other case was a positive culture documented. Given the high rate of fever in patients treated with chemotherapy without a stem cell graft at this stage post treatment, the 2.73% incidence is the more accurate figure.

Thus, if the true rate of infection is applied, even using the high rate of 2.4% for contaminated samples reported by Webb et al, the actual number of potential lethal infections is:

$$8000 \times 0.024 \times 0.0273 \times 0.58 \text{ PBSC} = 3 \text{ patients.}$$

If the rate of 0.2% reported by Espinosa is applied, the number is:

$$8000 \times 0.002 \times 0.0273 \times 0.58 \text{ PBSC} = 0.25 \text{ patients.}$$

These numbers are strikingly lower than the 15 patients quoted by the FDA.

Thirdly, it must be noted that the added inpatient costs for treatment of these infections are grossly inaccurate, since each of these patients would be expected to be in the hospital as an inpatient during the same time to receive support following myeloablative therapy.

I will not reiterate the cost accounting provided by FAHCT in its assessment of the added costs of the FDA rules beyond those incurred by practices already required by FAHCT for accreditation. Suffice it to say they are significantly higher than the FDA estimates and likely not sustainable by smaller centers.

In summary, while we applaud the efforts of the FDA, and appreciate their responsiveness to FAHCT as reflected by the similarities between the proposed FDA rules and the existing FAHCT standards and guidelines, we cite several new rules that will have a negative and potentially severe impact on the clinical practice of transplantation. By placing unduly burdensome requirements on transplant collection centers, certain of these rules may also force the closing of many small collection centers in the United States and likely limit access to hematopoietic stem cell transplants for patients in our own and other countries participating with the National Marrow Donor Program. The latter problem is particularly worrisome since it would reduce the potential pool of unrelated donors for its current level of 7 million to 4 million, and deny hundreds of patients a potentially curative graft. Lastly, we question the risk/benefit ratio proposed since, 1) the actual rates of contamination of stem cell transplants cited do not exceed those reported for unmanipulated platelet and red cell transfusion, 2) the number of severe infections to be presented is strikingly smaller than estimated and, more importantly, not likely to be affected by the rules proposed and, 3) the additional costs, which are not likely to be deferred by third party insurers, are exorbitant.

We respectfully suggest that the rules cited in this letter be deleted or modified. We also suggest that the existing guidelines required by FAHCT are sufficient to insure the safety of hematopoietic stem cell transplants we all wish to provide.

Thank you for your consideration.

Sincerely yours,

Richard J. O'Reilly, M.D.
President, American Society for Bone Marrow Transplantation

# FAHCT Letter to the Food and Drug Administration

May 7, 2001

Food and Drug Administration Docket
Dockets Management Branch
HFA-305
Food and Drug Administration
5630 Fisher's Lane, Room 1061
Rockville, MD 20852

**Re: 21 CFR Part 1271 [Docket No. 97N-484P]: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement**

The following is the response of the Foundation for the Accreditation of Hematopoietic Cell Therapy (FAHCT) to the Food and Drug Administration's proposed regulations for Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement published in the Federal Register on January 8, 2001.

In addition to the specific proposed regulations discussed in this letter, FAHCT and it's parent organizations, the International Society of Hematotherapy and Graft Engineering (ISHAGE) and the American Society of Blood and Marrow Transplantation (ASBMT), feel strongly that the risks from the contaminated hematopoietic progenitor cell (HPC) products and the costs of implementing the proposed regulations included in the 21 CFR Part 1271 document are highly flawed and misleading. As we discuss below, the risks to the patient are overstated and the estimates of the costs of complying with the proposed FDA regulations under-estimated.

**Risks of Contaminated HPC Products and Cost Estimates of Compliance**

The statements made regarding the morbidity and costs incurred because of contaminated hematopoietic transplant products are greatly exaggerated, misleading and fundamentally incorrect. Infections frequently occur following hematopoietic transplantation related to pancytopenia and are not due to contaminated PBSC. The costs involved with hematopoietic transplantation are directly related to supportive care required during the period of chemotherapy induced myelosuppression post transplant. Although contamination of the hematopoietic transplant may rarely occur in hematopoietic transplant collections, it generally involves relatively nonpathogenic skin flora. Since it is often not feasible to collect additional transplant products, and the transplant can be life saving, a number of cases have been reported using cells contaminated by S. epidermidis without major complication or prolongation of hospitalization; patients are generally treated with appropriate antibiotics during the cell infusion. The toxicity of DMSO is readily managed by limiting the amount of DMSO infused. ICU admissions in transplant recipients are generally the result of high dose chemotherapy and infections unrelated to contaminated cell infusions; it is well documented that these infections are acquired from flora colonizing the gastrointestinal and respiratory tracts, not contaminated transplant products. Thus the calculations regarding lives saved and costs reduced by the proposed measures are fundamentally flawed. We are unaware of evidence that methods currently in use by the medical community have resulted in avoidable morbidity or mortality.

**Specifically relating the FDA risk and cost estimates:**

1) FDA estimates that the average stay for a bone marrow transplant patient in 1994 was 35 days at a cost of $168,573. Costs and average length of stay in 2001 are much different than in 1994; again, this figure is related to generally supportive care needed for a transplant recipient and is not due to contamination of the graft.
2) The FDA attempts to estimate the impact of a contaminated HPC product for immunosuppressed recipients. The marginal risk of a contaminated product over that of infection from other causes in immunocompromised hosts is extremely small in aggregate. As indicated there are many reports of successful transplantation despite low level contamination of the graft.
3) The dimethylsulfoxide (DMSO) toxicity attributed to large volume peripheral blood progenitor cell infusions is overestimated. The use of DMSO has no impact on cost or toxicity in the vast majority of HPC recipients.
4) FDA estimates that 2.4% of peripheral blood progenitor cell products are contaminated and suggest there is a 13.7% incidence of infection in patients receiving contaminated HPC products (net infectious risk: 0.33%). The incidence of infection cited greatly overestimates the risk of infection caused by the HPC product. Further, the vast majority of contaminated HPC products contain skin flora (gram-positive cocci) that are not life-threatening, are easily treated in the outpatient setting, and do not contribute at all to inpatient hospital costs as suggested by the analysis. These infections almost never cause hospital admission or prolongation of hospital stay. In the same reference cited by the FDA,[1] there were **no** irreversible sequelae noted following infusion of contaminated product.
5) Intensive Care Unit (ICU) admission. The FDA cited data of a 57% death rate in transplant patients admitted to ICU with infections versus a 13% death rate in patients with no infections is **not** relevant to the cost of infusing contaminated HPC products, but rather the cost and risk of endogenously acquired infection in transplant patients. There are no data to suggest that patients who receive contaminated HPC products require ICU care or have a higher death rate than similar transplant patients who receive uncontaminated products. The FDA estimates that 15 patients a year could get infection from contaminated HPC products and that 7 of these patients would die. As noted above, death from contaminated product infusions is extremely rare. Of the estimated 15 patients, it is highly likely that the mortality will be zero and that no additional hospital days would be required for treatment. The anticipated additional cost per patient is less than $500

for the requisite two-week course of vancomycin or similar antibiotic. Transplant recipients generally receive antibiotic prophylaxis as a standard of care and thus, would not receive additional days of antibiotic treatment, even if a contaminated graft was administered. Thus, for an estimated cost of no more than $7500/yr, and no excess mortality risk, the agency proposes regulation costing millions of dollars per year (see below).

6) The FDA document states that the aggregate annual costs for a facility to come in to compliance with their proposed regulations would be $9,256.81. That calculation was derived from one-time costs of $3,571,049; annual costs of $3,194,292 and then total annualized costs of $3,702,027 calculated for 400 facilities. However, on page 1526, table 2, column 5, the costs of complying with the proposed regulations were broken down by specific regulation, for both compliant (i.e. FAHCT accredited) and noncompliant facilities. We took the FDA's estimated costs from table 2 and determined that for a compliant (FAHCT accredited) facility, the cost per facility per year would be $27,291 and for noncompliant facilities $79,437. The annual costs for 300 centers that were determined to be compliant would therefore be $8,187,300. For the 100 facilities estimated to be noncompliant, the cost would be $7,943,000. Thus the total annual costs of compliance would actually be $16,131,000. If this additional cost were associated with additional safety for the patients there would be less concern. However, as discussed below, there are no data to suggest that any of the proposed regulations, particularly for compliant facilities, would end up improving the safety and thus clinical care of our HPC transplant patients.

**The following proposed regulations are of concern to FAHCT:**

**1271.150 (b) paragraph 2: Facility responsible for release criteria**

Further clarification of who is responsible is required. It is not clear whether this responsibility pertains to the manufacturing facility or just the distributor. If the distributor is an institutional laboratory that receives a product that was processed at a commercial laboratory, this requirement would be unduly burdensome.

**1271.160 (b) Functions (7) paragraph 2: Confidentiality**

FDA is requiring in section Sec. 1271.160 (b)(7) that the periodic review and analysis of all product deviations be made available for review upon inspection and for submission to FDA upon request. Furthermore, FDA is requiring in section 1271.320(b) that a complaint file to be maintained shall also be made available for review and copying upon request from an authorized employee of the FDA.

Both the periodic audit of product deviations and the collation of a complaint file are tools of quality management. The proper conduct of quality management activities requires open and truthful review of adverse outcomes within the facility conducting the audit. FDA should state in the final rule that FDA and its employees shall guarantee that the confidentiality of these quality management activities will be strictly maintained by FDA and that records or copies of such records shall not become part of the public record regarding a manufacturer or distributor of cellular or tissue-based products.

**1271.160 (c) Authority over program**

This is a departure from the requirements that the agency has imposed on other areas such as blood and blood components, where the more general wording of the regulation [21CFR 606.100 (b) (19) (c)] may on occasion lead to a single person doing actual work and final review, separated in time and function. In small laboratories with only a single technician it may not be possible for an independent person to have oversight. This requirement will limit access to care by limiting the number of programs available who could provide additional staffing. The proposed tissue regulation is at least as stringent as cGMP requirements in 21CFR 211.

**1271.160 (d) Audits (2) Acceptable personnel**

As above, in small laboratories with only a single technician, there may not be an alternative knowledgeable person able to perform the audits. We think it would be inappropriate to limit access to care by limiting programs that had a knowledgeable staff person but not another knowledgeable person to perform the audit.

**1271.170 Organization and personnel (b) Competent performance of functions**

We recommend that "training and documentation of competency" be used rather than "education and experience." The latter are more vague and do not ensure competent performance of the procedure.

**1271.180 Procedures (6) Deviations**

Some deviations, such as those occurring in process, cannot be authorized in advance.

**1271.180 (last sentence) Archiving records for at least 10 years**

This requirement to maintain obsolete procedures for ten years is inconsistent with record retention requirements where documents pertaining to manufacture of a product should be kept for at least 10 years after implantation, transplantation, infusion, or transfer of the product. [Section 1271.270 (e)]. We believe the longer retention of obsolete procedures (i.e., for ten years after transplantation) to be more appropriate and request clarification of FDA intent.

**1271.190 (c) Facilities (4) Cleaning and sanitation activities**

Clarification of "significant" cleaning and sanitation activities is necessary. Such activities could include mopping the floor or washing the cabinets. We believe it would be unduly burdensome to keep records of mopping the floor for 10 years.

Alternatively, changing the air handling filters is a significant cleaning activity that would have more relevance to the quality of the processing procedures and records of such an activity warrant retention.

**1271.195 Environmental control and monitoring (3) Cleaning/disinfecting rooms**

We interpret this to mean that this type of cleaning and disinfection would not apply to most stem cell laboratories performing routine (minimally manipulated) processing procedures. If that is not the case, it is burdensome to require disinfection of all rooms when other control systems to prevent contamination are in place.

**1271.195 (5) Environmental monitoring for "organisms"**

There is no consensus from current expert opinion on what "organisms" to monitor. This regulation would have to be more specific to be meaningful.

**1271.200 Equipment (c) Calibration of equipment**

We object to the requirement for calibration of computers since they do not measure anything. Validation should be sufficient.

**1271.200 (e) Records (2nd sentence) Records of recent maintenance, cleaning, etc.**

Such records cannot physically be kept on small instruments such as pipettes. A central repository of such records should be sufficient.

**1271.200 (e) Records (3rd sentence) Records of the use of each piece of equipment**

The instrument used to process a product is already documented on the processing record. To require listing each product process for each piece of equipment does not add to the safety or quality of the product and is unnecessarily burdensome.

**1271.210 Supplies (c) Records (3) Records of each supply or reagent**

The supplies and reagents used to process an HPC product are already on the processing record. As above, to require listing each product process for each pipette or bottle of medium does not add to the safety or quality of the product and is unnecessarily burdensome.

**1271.220 Process controls (b) Processing material**

It is not always physically possible to document that the processing material has been removed from the product. For example it is not possible to determine exactly how much ficoll is left in the HPC product to be issued. It should be sufficient to document that validated procedures were used in processing.

**1271.210 (c) Pooling of human cells from two or more donors**

This requirement conflicts with the philosophy of the regulatory model which holds that, as technology becomes more standard, the requirements become less burdensome, not more.[2] Although currently generation of cellular products such as cytoxic T lymphocytes or dendritic cells are typically performed under IND, this may not be the case as these procedures become more standard. Such a requirement will stifle technology transfer and ultimately impact adversely on patient care.

**1271.250 Labeling controls (3) Documentation required for distributed HPC products**

"Distribution" needs to be defined. If the product is going from the HPC laboratory to the clinical unit of the same program, detailed documentation of the donor testing does not need to accompany that product as it can be found in the laboratory. It is burdensome to include all the specific results of the testing and doesn't improve the quality of the product. It is sufficient to provide the statement of suitability including the specifics only when there is a product deviation. If distribution means distribution outside of the institution then such documentation makes more sense.

**1271.260 Storage (b) Temperature (2) Temperature limits**

All three parameters (ensuring function and integrity, preventing deterioration, and inhibiting infectious agent growth) may not be optimal at the same temperature, and in fact are likely to be optimal at different temperatures. Some HPC products are held at room temperature in the absence of preservatives or antibiotics. That temperature might be optimal for preserving integrity and function, but allow growth of some infectious agents. Each facility will have to prioritize those three parameters and develop standard operating procedures that describe the acceptable temperature limits for the products in their own institution, based on their own validation to ensure integrity, etc.

**1271.260 Storage (c) Expiration date**

The safe duration of cryopreservation for an HPC product is unknown at this time and will take years to validate.

**1271.270 Records (c) Other record keeping requirements (5th sentence) Donor suitability records in English**

Clarification is required here, as clearly English translations would not be required for foreign facilities that are processing products to be distributed outside the United States. This should be stipulated for products distributed within the United States.

**1271.290 Tracking (d) Product information**

The manufacturer has no authority over the content of the medical record. It should be sufficient to provide paper documentation appropriate for the medical record and notice of the Federal Regulations requiring that the information be placed in the medical record.

**1271.290 (f) Consignees**

The manufacturer has no authority over the content of the medical record and may not have permission to review the content of the record at a later time. It should be sufficient to provide the paper documentation appropriate for medical record in notice of the Federal Regulations requiring that the information be placed in the medical record.

**1271.320 (b) Complaint file (3rd sentence) File review and copying by the FDA**

Copying files is a breach of confidentiality that is not acceptable. If this is required, the FDA must ensure that patient-specific information does not become part of the public record.

FDA is requiring in section Sec. 1271.160 (b)(7) that the periodic review and analysis of all product deviations be made available for review upon inspection and for submission to FDA upon request. Furthermore, FDA is requiring in section 1271.320(b) that a complaint file to be maintained shall also be made available for review and copying upon request from an authorized employee of the FDA.

Both the periodic audit of product deviations and the collation of a complaint file are tools of quality management. The proper conduct of quality management activities requires open and truthful review of adverse outcomes within the facility conducting the audit. FDA should state in the final rule that FDA and its employees will guarantee that the confidentiality of these quality management activities will be strictly maintained by FDA and that records or copies of such records shall not become part of the public file regarding a manufacturer or distributor of cellular or tissue-based products.

**1271.350 Reporting (a) Adverse reaction reports (1) Adverse reaction information (iv) Medical or surgical intervention**

This requirement is too vague and nonspecific. Medical intervention could be giving Benadryl and Tylenol. Requiring this type of intervention to be reported is overly burdensome and will not improve the quality of the HPC product or patient care in general.

**1271.350 (b) Reports of product deviations (1)**

Reporting minor and unimportant deviations should not be required. More specifics on how serious a deviation needs to be to require reporting should be provided.

**1271.420 Human cellular and tissue based products offered for import (b) Holding products until release**

It is medically unsafe to hold fresh HPC products that would need to be processed and infused without cryopreservation, for FDA review. This requirement is not logistically feasible, and has a high chance of jeopardizing the quality of the products and thus seriously compromising transplant patient care. This would require that the FDA be available 24 hours a day 7 days a week to deal with HPC products coming from overseas. Even those products that are cryopreserved will have limited duration before thawing occurs; the FDA could ultimately be responsible for adversely affecting the integrity and function of the products.

In summary, it appears that the proposed FDA regulations offer little additional benefit over the FAHCT Standards that are currently in place. Given that FAHCT is already inspecting to standards which are very close to the proposed regulations we once again offer our services to improve the quality of care and HPC products provided to our patients. We look forward to continued dialog on this and other issues.

Sincerely,

Elizabeth J. Shpall, MD, *President*, *FAHCT*
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Frank Smith, MD, *Board Member*, *FAHCT*
Richard O'Reilly, MD, *President*, *American Society for Blood and Marrow Transplantation*
Robert Negrin, MD, *President*, *International Society for Hematotherapy & Graft Engineering*

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